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The Benefits and Challenges of Setting up a Longitudinal Psoriatic Arthritis Database

Dafna D. Gladman, Laura C. Coates, Deepak R. Jadon, William Tillett, Philip Mease, Marijn Vis

ABSTRACT: The members of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have shown great interest in developing a common GRAPPA database. To address this interest, GRAPPA included a symposium at its 2017 annual meeting to examine the concepts of registries and databases. At this symposium, examples of existing databases were reviewed and their challenges and achievements were discussed.

Key Indexing Terms: Databases, Psoriasis, Psoriatic Arthritis, Registries, Prognosis, GRAPPA

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Author Information: DD Gladman, MD, FRCPC, Professor of Medicine, University of Toronto, Senior Scientist, Krembil Research Institute, Director, Psoriatic Arthritis Program University Health Network, Toronto Western Hospital, Toronto, Ontario, Canada, dafna.gladman@utoronto.ca; LC Coates, MBChB, PhD, Department of Orthopedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, laura.coates@ndorms.ox.ac.uk; DR Jadon, MBBCh, MRCP, PhD, Consultant Rheumatologist, Department of Rheumatology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, deepak.jadon@addenbrookes.nhs.uk; W. Tillett, MBChB, PhD, Consultant Rheumatologist, Royal National Hospital for Rheumatic Diseases, Senior Lecturer, University of Bath, Bath, United Kingdom, w.tillett@nhs.net; PJ Mease, MD, Rheumatology Research, Swedish Medical Center and University of Washington School of Medicine, Seattle, Washington, USA, pmease@philipmease.com; M Vis, MD, Department of Rheumatology, Erasmus Medical Center, Rotterdam, The Netherland, marijn.vis@erasmusmc.nl

Corresponding Author: Dafna Gladman, MD, FRCPC, Toronto Western Hospital, 399 Bathurst Street, 1E-410B, Toronto, Ontario, Canada, M5T 2S8; phone 416 603 5753; fax 416 603 9387; email dafna.gladman@utoronto.ca

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Psoriatic arthritis (PsA) is a complex condition characterized by a variety of clinical manifestations and disease courses. As with other similar conditions, the best way to understand the course of disease and patient prognosis is through observational cohort studies. These studies depend on the prospective collection of data on a large number of patients followed according to standard protocols.(1) At the GRAPPA 2017 annual meeting in Amsterdam, The Netherlands, examples of existing databases were reviewed and their challenges and achievements were discussed.

Dr. Dafna Gladman (Toronto, Ontario, Canada) discussed the differences between registries and cohorts. She stated that there are several types of registries, including administrative registries, registries for clinical trials, registries for genetic studies, registries for biologics, and registries for longitudinal observational studies.

Administrative registries are set up for administrative purposes to record patients with individual diagnoses and usually do not include detailed information about individual patients or their disease course. Some contain information on medications, hospitalizations and health care utilization. Moreover, the validity of the diagnosis is often unproven. Registries for clinical trials record patients with the disease in question and include only the minimum information necessary to determine whether a patient is eligible for a clinical trial. Registries for genetic studies include patients with a particular disease (and usually also include healthy controls) and include minimal disease process information, but detailed genetic analyses information. Registries for biologics usually include only the minimum information necessary to determine therapy response and any particularly adverse events that relate to the therapy. Registries for longitudinal observational studies usually include more detailed information and are generally considered databases as opposed to registries (Table 1). Compared to clinical trials, longitudinal databases include all patients, record all drugs, provide long-term observation with a large sample, have inclusive information, and record all possible outcomes. Thus, databases provide the prospective collection of data from a large number of patients and use standardized

protocols, including clinical, laboratory, imaging, and genetic data. These data are collected over a long observation period, which allows for varied presentations and courses to be analyzed. In addition, databases require computer tracking of all information. This allows for the description of disease course and long-term medication complications, the understanding of pathogenesis, and the study of associations between disease course and drug therapy. In addition, this provides insight into disease progression and allows researchers to plan for future trials.

To gain the most benefit from databases and to be able to replicate or increase the power of specific observations, it is important that similar registries have the same information collected in a similar way. Thus, clinical and laboratory assessment should be confirmed to be similar and the consistency of variables must be assured. The actual platform need not be the same as long as harmonization between items is confirmed. Whatever database platform is used, it must allow for the easy transfer of data to a statistical system for data analysis.

It is important to avoid selection bias and demonstrate internal and external validity. Methods of observation and measurement must be clearly defined, and complete follow-up should be attempted to avoid information bias. It is also important to consider confounding factors such as time and intervention, although these may be overcome by design and analysis.

Dr. Gladman provided an example of the database from the University of Toronto Psoriatic Arthritis Program. The Toronto cohort currently includes 1450 patients and has been operating since 1978. Patients are assessed at 6-12 month intervals according to a standard protocol.(2) The reliability of joint assessment has been proven through a number of studies,(3, 4) and the radiographic method has also been proven reliable.(5) In addition, patients lost-to-follow-up and those followed regularly had similar disease characteristics at presentation.(6)

Dr. Gladman highlighted the challenges of setting up a computer database, including quality assurance, data entry costs, issues with exporting data for statistical analysis, and the

large number of staff required to maintain a database. Nonetheless, the database provided substrate for multiple investigations.

Current and Proposed PsA Cohorts

Dr. Marijn Vis (Rotterdam**,** The Netherlands) discussed the Dutch cohort of PsA, which is comprised of 40 rheumatologists from 11 hospitals in the southwest of The Netherlands. The Dutch cohort's mission is to improve care for patients with psoriatic arthritis through education, research, and standardization. To set up their database, the Dutch cohort involved rheumatologists and patients with unmet needs who set up a clinical and science committee. Members contributing to the cohort own their own data. If possible, lab results, medication, and other data are taken directly from the hospital data warehouse with patient questionnaires completed online. These data are all imported into one database. Data warehouses are used to store data from the hospitals' electronic patient files, and data collection is currently semi-automatic. To date, there are over 500 patients included in this database. In addition to the scientific use of data, the data will also be used, together with the automatic data import, to create a support tool for clinical care. The aim is to develop a decision support system to assist physicians in using the appropriate treatment for the right patient based on the information collected in the database.

Drs. Laura C. Coates (Oxford, United Kingdom), William Tillett (Bath, United Kingdom), and Deepak Jadon (Cambridge, United Kingdom) presented a collaboration from the United Kingdom (UK) that will establish a cohort with embedded trials using a new methodology. This cohort will recruit patients from Oxford, Bath, and Cambridge starting in 2018. The Trials within Cohorts (TWiCs) or cohort multiple randomized controlled trial (cmRCT) design will be used and was first published in 2010. This method recruits a central cohort having "treatment as usual" with regular observations and then adds pragmatic trials of alternative therapies. Eligible patients for trials are identified in the cohort and randomized to the offer of an intervention or to remain as controls in the cohort.

This design is particularly useful for open-label efficiency comparisons of therapeutic interventions with “treatment as usual” as the comparator. It is ideal for chronic conditions and where expensive desirable treatments are being trialed. It allows robust generalizability from studies to routine health care, avoids attrition and disappointment bias from controls in open label studies as patients only receive information relevant to their care, aids recruitment to trials, allows routine collection of long-term outcomes, and increases efficiency with multiple trials within one cohort.(7)

In collaboration, members of the group are establishing a cohort of early PsA patients who will all receive step-up treatment guided by a treat-to-target (T2T) approach. This will form the central cohort and will collect outcome data on a real-world feasible T2T model. At present, two interventional trials are planned: the first in mild PsA with low disease impact where patients will not be prescribed the usual disease-modifying therapy, and the second in moderate-severe PsA where patients will be offered more aggressive therapy.

A number of TWiCs studies are currently running across Europe with the majority in the oncology field. The UK cohort study will be the first in rheumatology and also one of the first TWiCs studies testing investigational medicinal products. This has required appropriate liaison with regulators during protocol development. There are challenges, including ethical and GCP issues with consent, and also that data collection must balance the robustness necessary for clinical trial and feasibility for regular clinic. Many people are unfamiliar with the TWiCs concept, which has made it important to connect and educate university staff, charity and industry funders, clinical trials units, and ethics and medicines regulatory authorities.

In Oxford, the cohort will be new and has been established specifically as a TWiCs study. In Cambridge, the cohort is new. In Bath, the cohort is pre-existing. Discussions between the three centers have aligned outcomes and time-points for data collection to allow this collaboration.

Dr. Deepak Jadon (Cambridge, United Kingdom) is harmonizing a group of 750 PsA cases, historically looked after by 10 consultants at the Addenbrooke's Hospital, into a single cohort looked after in a dedicated PsA service that started in 2015. Using the EPIC platform, clinical data are collected to an electronic patient record system. In late 2017, electronic tablets will be used to collect patient reported outcome measures (PROM) in the clinic waiting area and from home. The cohort includes both inception patients and prospective, established PsA patients. The program includes a consultant, research fellow, resident, research nurse, and PsA specialist nurse. The program takes direct referrals from general practitioners, dermatologists, gastroenterologists, ophthalmologists, and internal referrals. All patients undergo a protocoled series of PROMs, examination indices, imaging, and laboratory tests. Patients have the opportunity for education and counselling about their condition as well as management by the PsA specialist nurse and doctors. They also have the opportunity to attend 6 monthly patient and family education evenings hosted by Dr. Jadon.

In keeping with GRAPPA recommendations for the management of PsA,(8) multispecialty working has been a tenant of providing a holistic PsA service. In 2016, a monthly dermatology-PsA multi-disciplinary team (MDT) meeting, 2 monthly inflammatory bowel disease (IBD)-spondyloarthritis MDT meetings, and 2 monthly hepatology-PsA MDT meetings were established. These MDT meetings are attended by consultants, trainees, fellows, and specialist nurses. Complex patients, diagnostic conundrums, and treatment escalation are discussed, with a view to ensuring more harmonized care of the multiple facets of psoriatic disease. The MDTs have also forged screening initiatives for PsA in PsC patients and for spondyloarthritis in IBD patients. The challenges of setting up this PsA service have included optimizing patient flow between the MDT, internet technology solutions to enable direct referrals to the PsA clinic, funding and implementing the electronic data collection initiative using tablets, funding dedicated PsA staff and job planning, and convincing commissioners and funders of the clinical and economic virtues such a service provides to both patients and the hospital.

Dr. William Tillett (Bath, United Kingdom) presented a historical perspective on the Bath PsA cohort and the opportunities and challenges of integrating a new TWiCs cohort into an established cohort database. The Bath PsA cohort was set up in 1989 by Professor Neil McHugh to answer questions about the PsA disease pathogenesis, clinical manifestations, prognostic indicators, the natural course of disease, and the real world effect of treatment. The cohort is a secondary-care cohort primarily serving the local community (95%) with 5% of participants coming as tertiary referrals from farther afield in the UK. As such, the cohort broadly represents patients with PsA in the UK. Patients are recruited to the cohort with any disease duration, including both new and established diagnoses (thus, it is not purely an inception cohort). In addition to a baseline set of data, clinical, patient-reported, and radiographic data is collected at routine clinical reviews (every 3 months for patients with active disease and every 6 months for those with more stable disease). Additional cross-sectional and longitudinal sub studies have been undertaken to answer specific questions over the last 28 years. Patients and clinicians have historically collected data on paper, and this data is then scanned into a database where it is monitored and validated by a database team.

Ensuring that the cohort fulfils the most up-to-date PsA classification criteria has been an important consideration over time. Initially, entry to the cohort was based on physician diagnosis, then the application of Moll and Wright criteria, and finally retrospectively applying CASPAR classification criteria.(9) Several milestones have necessitated changes to the data collected such as the introduction of biologic therapies, the need for more clinical and mediation data collection and development, and changes to the Outcome Measures in Rheumatology (OMERACT) Core set of domains as measures in randomized controlled studies and longitudinal observational studies.(10, 11)

The decision to set up a new TWiCs subcohort in Bath coincided with a recognition of the importance of moving to electronic data capture and integration with other clinical systems to widen the routinely collected research data. It became clear after discussions between

Oxford, Cambridge, and Bath that having a single data collection platform across sites would not be achievable with the different organizations' funding priorities and existing contract commitments. The solution was to avoid real-time data upload and instead upload study data from existing systems at set time points during the study. A decision was made to harmonize datasets based on the OMERACT core set using the best validated and most feasible measures. Feasibility of data collection was a significant consideration as each site has different clinic structures and staff resources. A dataset that could be achieved at each site was negotiated.

Prior to the open discussion about cohorts, Dr. Philip Mease (Seattle, Washington, USA) discussed the Corrona Registry, a consortium of investigative centers in the United States that began as a registry for rheumatoid arthritis and PsA but more recently added patients with spondyloarthritis.(12) The Corrona Registry collects detailed information on clinical disease manifestations, including enthesitis, dactylitis, spine and skin disease, comorbidities, and the treatment of these diseases. This registry, however, only captures imaging data as done in practice and has no biobanking component. This registry has generated a number of recent publications.(13-15)

During the discussion, GRAPPA members were interested in the difficulties of setting up the cohorts, the financial considerations, as well as the feasibility of collecting detailed information on all patients.

GRAPPA members have expressed interest in developing a GRAPPA database, a concept that was further discussed during the research meeting that followed the 2017 GRAPPA annual meeting.

Table 1: Information collected in different registry types

Type of Registry	Information collected
Administrative	Demographic
Clinical Trials	Demographic plus some clinical information especially drugs
Genetic Studies	Proband and family information including enough details to define a phenotype together with genetic information
Biologic Registries	Demographic, clinical, and therapeutic information to determine response and adverse events
Cohort Database	As much detail as possible to follow disease progression and identify new features

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